

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Manne Satyanarayana REDDY et al.

Art Unit: 1625

Application No.: 10/647,449

Examiner: C.C. Chang

Filed: August 25, 2003

For: POLYMORPHIC FORMS OF (S)-REPAGLINIDE AND
THE PROCESSES FOR PREPARATION THEREOF

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

SUPPLEMENTAL REPLY BRIEF

This paper is submitted in response to the Corrected Examiner's Answer mailed November 18, 2007, for the above-identified application, and correcting Office Communication mailed December 7, 2007. Submission of a reply brief in response to the Examiner's Answer is due by February 7, 2008. Accordingly, this reply brief is being timely filed.

1. **Status of the Claims**

Claims 1-57 were finally rejected in an Office Action mailed on March 6, 2006. Claims 3, 39, 49, 52 and 55 were canceled in an amendment submitted on December 1, 2005. Accordingly, claims 1-2, 4-38, 40-48, 50, 51, 53, 54, 56 and 57 are considered to be the subject of this appeal.

2. **Grounds of Rejection for Review on Appeal**

A. Whether claims 38 and 40-48 are anticipated under 35 U.S.C. § 102(b) by Grell et al (U.S. Patent No. 5,312,924; "Grell I").

B. Whether claims 1, 34 and 35 are anticipated under 35 U.S.C. § 102(b) by Grell I.

C. Whether claims 1, 2, 4-37, 50, 51, 53, 54, 56 and 57 are unpatentable under 35 U.S.C. § 103(a) over Grell I in view of Grell et al. (*J. Med. Chem.*, 1998, 41:5219-5246; "Grell II") and Brittain, ed. (Polymorphism in Pharmaceutical Sciences, 1999, pp. 179-79, 185, 219; "Brittain").

D. Whether claims 8-18 are invalid under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement.

3. Argument

A. Incorporation By Reference

The present appeal had been briefed previously. On September 6, 2006, the Applicants filed an Appeal Brief from the final rejection mailed on March 6, 2006. The Examiner's Answer was mailed on November 30, 2006. Applicants filed a Reply Brief on January 29, 2007. Supplemental Examiner's Answer was mailed on February 26, 2007. Applicants filed a Supplemental Reply Brief on April 25, 2007. The appeal has been returned to the Examiner by the Board of Patent Appeals and Interferences on August 28, 2007 due to deficiencies in the grounds of rejection. The Examiner mailed Corrected Examiner's answer on November 18, 2007 and an Office Communication with corrections on December 7, 2007.

In this paper, the Reply Brief filed on January 29, 2007 and the Supplemental Reply Brief filed on April 25, 2007 are incorporated by reference in their entirety with respect to grounds of rejection A, B, C, and D. In addition, Applicants make reference to the recent decision of the Board of Patent Appeal and Interferences in *Ex Parte Buchi*, 2007 WL 2745815 (September 6, 2007). Applicants assert that *Ex Parte Buchi* has direct bearing on the resolution of issues in the present appeal. Applicants request consideration of the additional arguments set forth below.

B. Additional ArgumentA. Rejection of Claims 38 and 40-48 Under 35 U.S.C. § 102(b)

Applicants reiterate the arguments made with respect to this ground of rejection in the Reply Brief filed on January 29, 2007 and the Supplemental Reply Brief filed on April 25, 2007 and incorporated by reference herein.

B. Rejection of Claims 1, 34 and 35 Under 35 U.S.C. § 102(b)

Claims 1, 34 and 35, directed to Form III of (S)-repaglinide, stand finally rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Grell I. The Examiner points to col. 16, Fig. 4 and col. 33, Form A, alleging that the polymorphic form disclosed therein is identical to the Form III recited in the rejected claims. See Corrected Examiner's Answer, at page 5, line 3. It is unequivocally clear from the Grell I's disclosure as a whole that Grell I's solid forms disclosed at col. 16, Fig. 4 and col. 33, Form A are solid forms of racemic repaglinide, which is a different chemical compound. The Grell I specification makes clear distinctions throughout between racemic and enantiomerically pure compounds, which are disclosed in separate parts of the voluminous specification. Compare, e.g., Example 11, col. 32 ("2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl}-aminocarbonylmethyl]-benzoic acid") and Example 12, cols 89-90 ("(S)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl}-aminocarbonylmethyl]-benzoic acid [emphasis added]"). The disclosure of a polymorph of a racemic compound does not anticipate claims to a polymorph of an enantiomer.

The latter portion of the disclosure of Grell I (Example 12, cols. 89-90) indeed refers to (S)-repaglinide. If the Examiner is to set forth a *prima facie* case of inherent anticipation over Grell I, there should be an allegation that the solid form disclosed in Example 12, cols. 89-90 is identical to the Form III of (S)-repaglinide of the rejected claims.

The evidence of record unequivocally shows that the solid form of Example 12 of Grell I and the Form III of the rejected claims are different polymorphs. Grell I's solid form has melting point of 126-128 °C (Grell I, col. 90, line 9), whereas the melting point for the Form III of the rejected claims is 79-84 °C (e.g., instant specification, at page 27,

Example 6). Grell I's solid is crystallized from ethanol or ethanol/water (Grell I, col. 90, line 7), the Form III of the rejected claims is crystallized from dichloromethane/petroleum ether (e.g., instant specification, at page 27, Example 6).

Even if the evidence of record were ambiguous (and it is not), to establish a *prima facie* case of inherent anticipation the Examiner must show scientific rationale or objective evidence tending to show inherency. See MPEP §2112. See also *Ex parte Buchi*, 2007 WL 2745815, at 4. Only then the burden will shift to the Applicants to disprove the inherency. See *id.*, citing, *Ex Parte Skinner*, 2 USPQ.2nd (BNA) 1788 (BPAI 1986). See also *Ex parte Havens*, Appeal No. 2001-0091, Sl. Op., at 3-5.

As mentioned above, *Ex parte Buchi* has direct bearing on the present appeal. In the present case, as in *Buchi* and *Havens*, the evidence adduced by the Examiner does not justify shifting of the burden. While Grell I discloses a crystalline form for (S)-repaglinide, the rejected claims recite a particular polymorph. What are the grounds for the Examiner's belief that the polymorph of Grell I is identical to the claimed polymorph? The Examiner alleges similarity in the infrared spectra ("IR"). However, none of the IR spectra set forth in Grell I relate to (S)-repaglinide. Rather, they pertain to a racemic compound. This is clear from the specification. See Grell I, col. 32, Ins. 55-63. As in *Buchi* and *Havens*, the Examiner did not provide a reason why the burden should shift to the applicants, and therefore did not set forth a *prima facie* case of inherency.

Further, to establish inherency, the reference's teachings or extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and it would be so recognized by persons of ordinary skill." See *In re Robertson*, 49 U.S.P.Q.2d (BNA) 1949, 1950-51 (Fed. Cir. 1999), cited in MPEP §2112. What would be the objective evidence of inherency? Why would one skilled in the art recognize that the procedure in *Grell I* would necessarily result in the claimed polymorph of (S)-repaglinide?

Accordingly, Appellants maintain that claims 1, 34 and 35 are not anticipated by Grell I under § 102(b), and the rejection should not be sustained.

C. Rejection of Claims 1, 2, 4-37, 50, 51, 53, 54, 56 and 57 Under 35 U.S.C. § 103(a)

Claims 1, 2, 4-37, 50, 51, 53, 54, 56 and 57 stand finally rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Grell I in view of Grell II and Brittain. The essence of the Examiner's assertions is that even if the polymorphic form is different, disclosure of a different polymorph of the same substance in the prior art renders claims to a new polymorph *prima facie* obvious. See, e.g., Corrected Examiner's Answer, at page 7 ("The instant specification and claims disclosed known compound S-repaglinide form III, which is the same pure substance as the prior art, only has different arrangements and/or different conformations of the molecule [emphasis as in the original]").).

However, such assertion is not supported by the current law. For example, in *Ex parte Buchi*, the claims to specific polymorphs were rejected over disclosure of a known crystalline form. 2007 WL 2745815, at 2. The Examiner in *Buchi* had made essentially the same argument, stating that "employment of a conventional obvious modification of a known process to obtain a pure form [...] is considered *prima facie* obvious in the absence of unexpected results." See *id.*, at 4. In response, the Board of Patent Appeals and Interferences did not support the automatic *prima facie* obviousness standard. See *id.* In fact, it is clear that the legal requirements for *prima facie* obviousness (e.g., disclosure of all claim elements and reasonable of expectation of success) are the law with respect to claims for polymorphic forms as well.

In *Buchi*, the Examiner cited Cheronis as a secondary reference to show that use of re-crystallization is well known in the art and finding obviousness of the basis of combining Cheronis with a primary reference that taught a crystalline solid. In other words, the Examiner in *Buchi* argued that since re-crystallization is known, an artisan would employ it to arrive at the claimed polymorph. The Board rejected this reasoning, stating that while one would be expected to purify by crystallization, "that would not necessarily lead to the claimed crystalline forms." *Id.*, at 5. This is no different than the situation in the present appeal.

As clear from the evidence of record, the present state of the art does not allow a prediction of existence of polymorphism for a particular drug product, let alone prediction of the specific polymorphic state. See, e.g., Goho and Bernstein articles. Clearly, an existence of one crystalline form of solid provides no reasonable expectation of success whatsoever to make any new polymorph, let alone to make the specific polymorph claimed. However, the presence of reasonable expectation of success with respect to modification of *Grell I* is the prerequisite of *prima facie* case of obviousness. See MPEP §2142.02, citing, *In re Rinehart*, 189 USPQ (BNA) 143 (CCPA 1976) ("Evidence showing there was no reasonable expectation of success may support a conclusion of non-obviousness.").

Accordingly, Appellants maintain that claims 1, 2, 4-37, 50, 51, 53, 54, 56 and 57 are not rendered obvious by *Grell I* in view of *Grell II* and *Brittain* under § 103(a), and the rejection should not be sustained.

D. Rejection of Claims 8-18 Under 35 U.S.C. § 112, First Paragraph

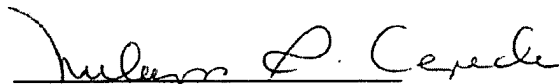
Applicants reiterate the arguments made with respect to this ground of rejection in the Reply Brief filed on January 29, 2007 and the Supplemental Reply Brief filed on April 25, 2007 and incorporated by reference herein.

Accordingly, Appellants maintain that no case for lack of enablement of claims 8-18 under § 112, first paragraph, has been made out, and the rejection therefore should not be sustained.

CONCLUSION

Appellants maintain that claims 1-2, 4-38, 40-48, 50, 51, 53, 54, 56 and 57 fully meet the requirements for patentability under §§ 102, 103 and 112. Accordingly, reversal of the Examiner's rejections is appropriate and is respectfully solicited.

Respectfully submitted,



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